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OLOMORASIB (LY3537982)

KRAS G12C INHIBITOR

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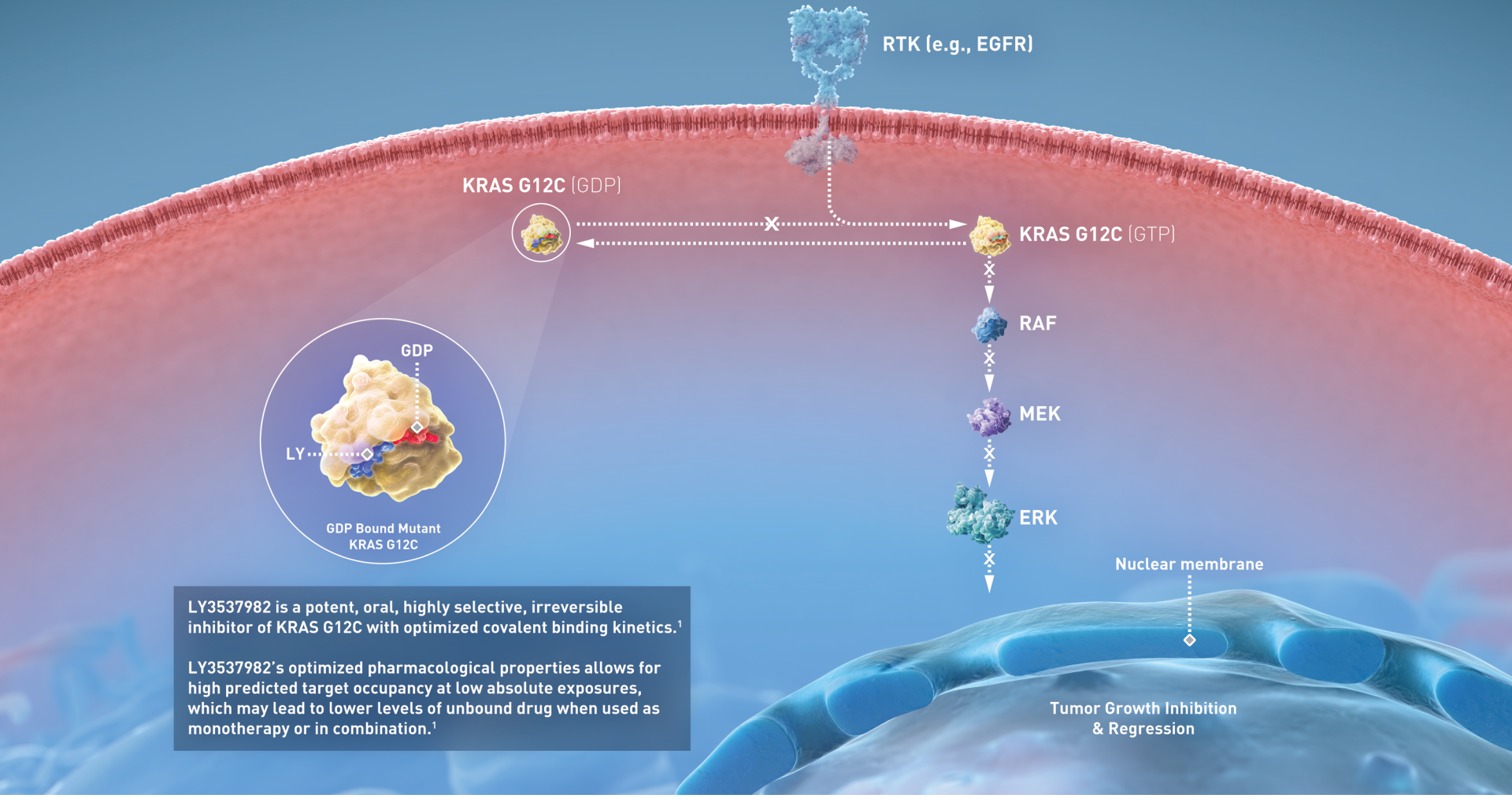
OLOMORASIB (LY3537982) | MECHANISM OF ACTION[1-4]



LY3537982 is a potent, oral, highly selective, irreversible inhibitor of KRAS G12C with optimized covalent binding kinetics.[1]

LY3537982's optimized pharmacological properties allows for high predicted target occupancy at low absolute exposures, which may lead to lower levels of unbound drug when used as monotherapy or in combination.[1]

References: 1. Peng SB, et al. *Cancer Res*. 2021;81(suppl 13):1259. **2.** Kano Y, et al. *Nat Commun*. 2019;10(1):224. **3.** Janes MR, et al. *Cell*. 2018;172(3):578-589. **4.** Ji J, et al. *Onco Targets Ther*. 2022;15:747-756.

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TARGET

KRAS is the most common oncogene across all tumor types. *KRAS G12C* represents a *KRAS* mutation in patients with non-small cell lung cancer (14%), colorectal cancer (3%), and other solid tumors (1%-3%).[1]

MOLECULE

Olomorasib is a selective covalent inhibitor of KRAS G12C; in preclinical models, it demonstrates activity as monotherapy and in combination with other anticancer therapies. It has competitive pharmacokinetic properties supporting its advancement into clinical testing. Olomorasib has been shown in vitro to target a KRAS G12C mutation, thereby inhibiting mutant KRAS-dependent signaling.[2]

CLINICAL DEVELOPMENT

Olomorasib is being studied in a clinical trial in patients with non-small cell lung cancer, colorectal cancer, or other solid tumors.

References: 1. Ji J, et al. *Onco Targets Ther*. 2022;15:747-756. **2.** Peng SB, et al. *Cancer Res*. 2021;81(suppl 13):1259.

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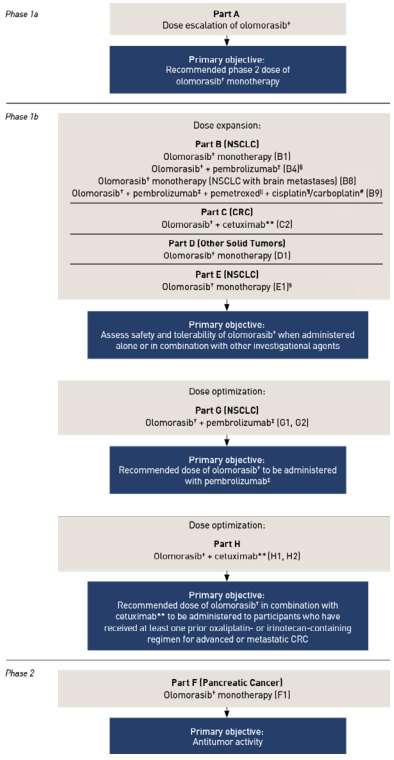
NCT04956640

A Phase 1/2 Study of LY3537982 in Patients With *KRAS G12C*-Mutant Advanced Solid Tumors*



* This clinical trial is being conducted globally.
† Olomorasib is administered PO.
‡ Pembrolizumab is administered intravenously (IV).
§ Prior *KRAS G12C* inhibitor allowed.
|| Pemetrexed is administered IV.
¶ Cisplatin is administered IV.
# Carboplatin is administered IV.
**Cetuximab is administered IV.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT04956640].

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NCT04956640

A Phase 1/2 Study of LY3537982 in Patients With *KRAS G12C*-Mutant Advanced Solid Tumors (cont.)

KEY INCLUSION CRITERIA

- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Evidence of *KRAS G12C* mutation in tumor tissue or circulating tumor DNA
- Histological or a cytologically proven diagnosis of locally advanced, unresectable, and/or metastatic cancer and meet cohort-specific criteria
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Adequate organ function
- Discontinued all previous treatments for cancer with resolution of any significant ongoing adverse events (AEs), except in certain scenarios
- Able to swallow capsules/tablets
- Agree and adhere to contraceptive use, if applicable
- For some parts of the study (eg, one of the two arms with olomorasib plus pembrolizumab and the arm of olomorasib plus pembrolizumab, pemetrexed, and platinum therapy), histologically or cytologically confirmed stage IIIB-IIIC or stage IV NSCLC that is previously untreated in the advanced/metastatic setting and not suitable for curative intent radical surgery or radiation therapy. Previously untreated patients who received adjuvant and neoadjuvant therapy are eligible if the last dose of the systemic treatment was completed at least 6 months prior to enrollment. For untreated patients in the arm with olomorasib plus pembrolizumab noted above, a single cycle of pembrolizumab may be initiated within 21 days prior to enrollment. For untreated patients in the arm of olomorasib plus pembrolizumab, pemetrexed, and platinum therapy, a single cycle of any or all of the drugs other than olomorasib may be initiated within 21 days prior to enrollment. Start of study treatment may be delayed to allow sufficient time for recovery from treatment-related toxicity
- For one part of the study, participants must have received at least one prior oxaliplatin- or irinotecan-containing regimen for advanced or metastatic colorectal cancer (CRC)

KEY EXCLUSION CRITERIA

- Disease suitable for local therapy administered with curative intent
- Active, ongoing, or untreated infection
- Serious preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study
- Serious cardiac conditions
- A second active primary malignancy or have been diagnosed and/or treated for an additional malignancy within 3 years prior to enrollment
- Symptomatic central nervous system (CNS) malignancy or metastasis and/or carcinomatous meningitis. Patients with treated CNS metastases are eligible for this study if their disease is asymptomatic, radiographically stable for at least 30 days, and they do not require treatment with steroids in the 2-week period prior to study treatment. This only applies to some parts of the study
- Prior treatment with any KRAS G12C small molecule inhibitor, except in certain scenarios where such prior therapy is allowed as per protocol
- The following patients will be excluded from some parts of the study:
  - Experienced certain serious side effects with prior immunotherapy
  - Have an active autoimmune disease that has required systemic anti-autoimmune treatment in the past 2 years
  - Have received a live vaccine within 30 days prior to the first dose of study drug
- Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 180 days after the last dose of study medication
- Known allergic reaction against any of the components of the study treatments

Please visit clinicaltrials.gov for more information on this clinical trial [NCT04956640].

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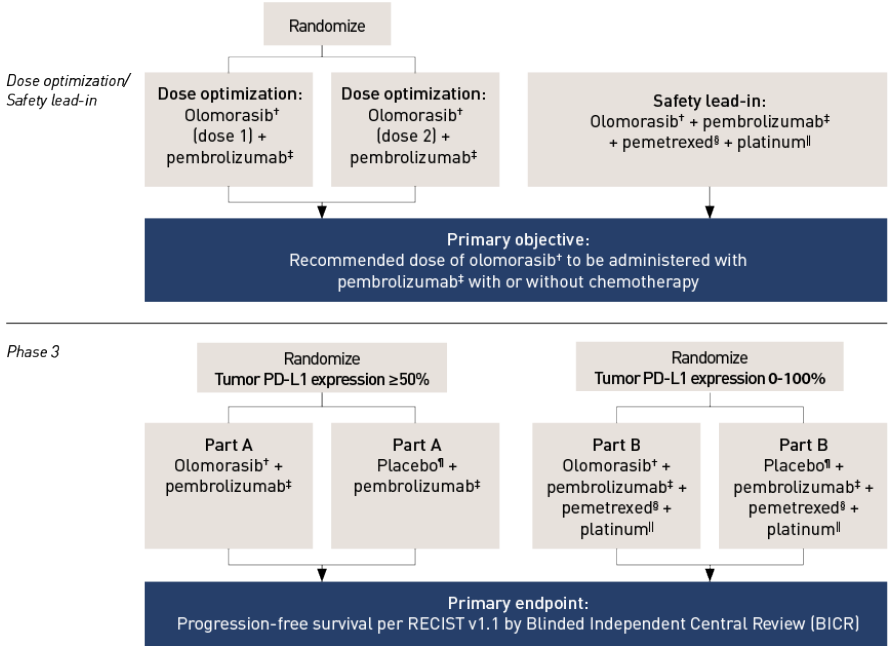
SUNRAY-01

A Global Pivotal Study in Participants With *KRAS G12C*-Mutant, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Comparing First-Line Treatment of LY3537982 and Pembrolizumab vs Placebo and Pembrolizumab in Those With PD-L1 Expression ≥50% or LY3537982 and Pembrolizumab, Pemetrexed, Platinum vs Placebo and Pembrolizumab, Pemetrexed, Platinum Regardless of PD-L1 Expression*



* This clinical trial is being conducted globally.
† Olomorasib is administered PO.
‡ Pembrolizumab is administered intravenously (IV).
§ Pemetrexed is administered IV.
|| Platinum (cisplatin or carboplatin) is administered IV.
¶ Placebo is administered PO.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06119581].

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SUNRAY-01

A Global Pivotal Study in Participants With *KRAS G12C*-Mutant, Locally Advanced or Metastatic Non-Small Cell Lung Cancer Comparing First-Line Treatment of LY3537982 and Pembrolizumab vs Placebo and Pembrolizumab in Those With PD-L1 Expression ≥50% or LY3537982 and Pembrolizumab, Pemetrexed, Platinum vs Placebo and Pembrolizumab, Pemetrexed, Platinum Regardless of PD-L1 Expression (cont.)

KEY INCLUSION CRITERIA

- Histologically or cytologically confirmed non-small cell lung cancer (NSCLC) with stage IIIB-IIIC or stage IV disease, not suitable for curative intent radical surgery or radiation therapy
- Part B and safety lead-in part B: the histology of the tumor must be predominantly non-squamous (in line with pemetrexed label)
- Disease with evidence of *KRAS G12C* mutation
- Known programmed death-ligand 1 (PD-L1) expression
  - Part A: ≥50%
  - Part B: 0%-100%
- Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Estimated life expectancy ≥12 weeks
- Ability to swallow capsules
- Adequate laboratory parameters
- Contraceptive use should be consistent with local regulations for those participating in clinical studies
- Women of childbearing potential must:
  - Have a negative pregnancy test
  - Not be breastfeeding during treatment and after study intervention for at least 180 days

KEY EXCLUSION CRITERIA

- A documented additional validated targetable oncogenic driver mutation or alteration in genes such as epidermal growth factor receptor *(EGFR)*, anaplastic lymphoma kinase *(ALK)*, *BRAF (V600E)*, human epidermal growth factor receptor 2 *(HER2)*, *MET* (exon 14), *ROS1*, rearranged during transfection *(RET)*, or neurotrophic tyrosine receptor kinase *(NTRK)*1/2/3
- Had any of the following prior to randomization:
  - Prior systemic therapy (chemotherapy, immunotherapy, targeted therapy, or biological therapy) for advanced or metastatic NSCLC
  - One cycle of standard-of-care treatment prior to study enrollment will be allowed for cases where immediate treatment is clinically indicated
- Central nervous system (CNS) metastases and/or carcinomatous meningitis
- For participants receiving pemetrexed and platinum (part B and safety lead-in part B):
  - Squamous cell and/or mixed small cell/non-small cell histology is not permitted
  - Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Is unable or unwilling to take folic acid or vitamin B_{12} supplementation

Please visit clinicaltrials.gov for more information on this clinical trial [NCT06119581].

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Pipeline information is current through February 6, 2024.

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